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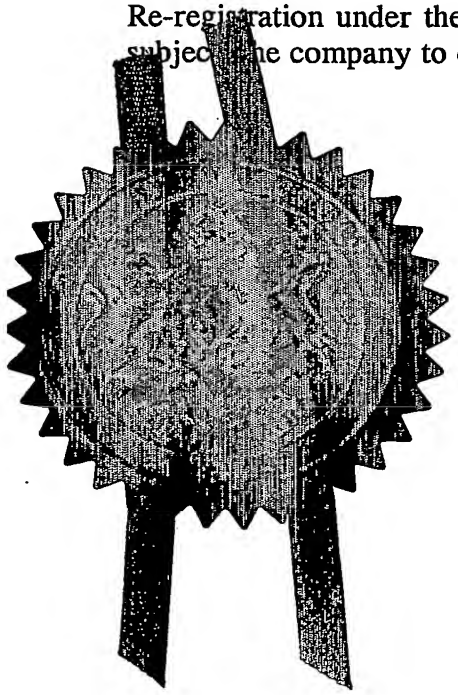
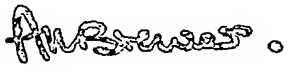


Signed 

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Cardiff Road
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1. Your reference — 100724

2. Patent application number *(The Patent Office will fill in this part)* — 0213267.8 — 11 JUN 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 7822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)*

Michael Andrew Nelson

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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Description	16
Claim(s)	01
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10. If you are also filing any of the following, state how many against each item.

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature (Authorised Signatory) Date 11/06/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer C Bennett - 01625 230148

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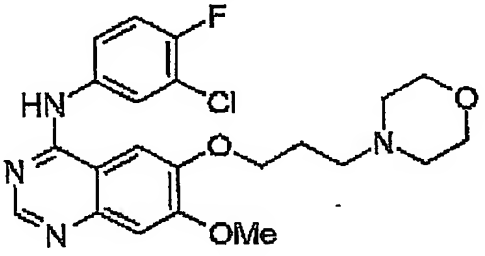
PHARMACEUTICAL COMPOSITION

The present invention relates to pharmaceutical compositions, more particularly to oral pharmaceutical compositions containing 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline or a pharmaceutically-acceptable salt thereof (hereinafter referred to as the "Agent").

The Agent is disclosed in International Patent Application WO 96/33980 (Example 1) and is a potent inhibitor of the epidermal growth factor receptor (EGFR) family of tyrosine kinase enzymes such as erbB1. The Agent has the structure of the Formula I



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and is now known as Iressa (registered trade mark), gefitinib (Unites States Adopted Name), by way of the code number ZD1839 and Chemical Abstracts Registry Number 184475-35-2.

The Agent possesses anti-proliferative activity such as anti-cancer activity and, accordingly, is useful in methods of treatment of proliferative disease such as cancer in the human or animal body. The Agent is expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by EGFR receptor tyrosine kinases, particularly cancers such as breast, lung, colon, rectum, stomach, prostate, bladder, pancreas and ovary and head and neck cancers. The Agent is currently in Phase III trials for the treatment of non-small cell lung cancer.

The Agent is a weakly basic compound and has two basic groups with pK_a's of 5.3 and 7.2. The protonation and deprotonation of these basic groups has a marked effect upon the solubility of the Agent in aqueous media. Consequently, the solubility of the Agent is highly dependent upon pH. For example, the free-base form Agent is soluble at pH 1 (10 to 30 ml of aqueous solvent required to dissolve 1g of Agent) but is practically insoluble above pH 7, with the solubility dropping sharply between pH 4 and pH 6 (≥10000 ml of aqueous solvent required to dissolve 1g of Agent at pH 6)

Compounds which have pH dependent solubility, particularly basic compounds, often exhibit undesirable pharmacokinetic properties such as problems in their absorption, possibly producing low or variable bioavailability between patients and between doses.

A factor which can affect the absorption of an orally administered drug is the changing pH experienced by the drug as it passes through the GI tract. Typically a drug may be absorbed in a number of different sites along the GI tract following oral administration for example, the cheek lining, stomach, duodenum, jejunum, ileum and colon. The pH may be different at each site of absorption with the pH significantly different from the stomach (pH 1-3.5) to the small intestine (pH 4-8). When the solubility of a drug varies with pH the drug may precipitate from solution as it passes through the GI tract. This can result in low absorption and/or variable adsorption between doses and different patients, because the drug needs to be in solution to be absorbed.

Although the Agent has a high solubility in the acidic environment of the stomach, it is not significantly absorbed from this area. The site of highest intrinsic absorption for the Agent is thought to be the upper intestine. However, in this region of the GI tract the pH is relatively high compared to that in the stomach and the Agent has a reduced solubility. As a result the Agent is prone to precipitate from solution as it passes from the acidic environment of the stomach to the higher pH environment of the lower GI tract, resulting in reduced and/or variable absorption of the Agent. This in turn may result in a high degree of inter-patient variability in the bioavailability and/or plasma concentrations of the Agent and possibly sub-optimal treatment efficacy in a proportion of patients. There is therefore a need to improve the pharmacokinetic properties of the Agent.

We have surprisingly found that the rate at which the Agent is precipitated from solution when the pH of the solution increases from a pH similar to that of the stomach to a pH similar that found in the lower GI tract, is significantly reduced when the Agent is formulated or administered together with certain excipients. This is expected to provide improved pharmacokinetic properties for example, increased absorption and/or bioavailability and may reduce inter-patient variability in the bioavailability and/or plasma concentration of the Agent, because the Agent remains in solution for longer in the region of the GI tract with the highest intrinsic absorption rates for the Agent.

According to a first aspect of the present invention there is provided a pharmaceutical composition comprising the Agent and a water-soluble cellulose ether.

By "water-soluble cellulose ether" is meant cellulose ethers that dissolve or disperse in water to give a colloidal solution or dispersion at a temperature of less than 30°C (for example from 10 to 20°C). Generally the water-soluble cellulose ethers will have a solubility in water of at least 20mg/ml, preferably at least 30mg/ml at a temperature of 10 to 20°C.

A suitable cellulose ether includes, for example hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and a water-soluble salt of carboxymethylcellulose (for example sodium carboxymethyl cellulose). Preferably the water-soluble cellulose ether is hydroxypropylmethyl cellulose (HPMC). A wide range of grades of HPMC may be used for example with a viscosity of < 60cps, such as from 2 to 18, preferably from 5 to 7cps, wherein the viscosity is measured in a 2%w/v aqueous solution of the HPMC at 20°C. The HPMC suitably has a degree of substitution of from 10 to 35% (preferably from 25 to 35%) by weight methoxy groups and 3-30% (preferably from 5 to 15%) by weight hydroxypropoxy groups. Preferred grades of HPMC include 2910, 1828, 2208 and 2906 (wherein the first two digits refer to the average degree of methoxy substitution and the second two digits to the average degree of propoxy substitution) as described in the Handbook of Pharmaceutical Excipients, 3rd Edition 2000 American Pharmaceutical Association p 252. More preferably the above grades of HPMC with a viscosity of from 2 to 18 cps (preferably from 5 to 7cps). It is especially preferred that the HPMC is grade 2910 with a viscosity of from 5 to 7 cps, wherein the viscosity is measured in a 2%w/v aqueous solution of the HPMC at 20°C.

Suitably, the weight ratio of the Agent to water-soluble cellulose ether is from 50:1 to 1:5, preferably from 35:1 to 1:1, more preferably from 33:1 to 2:1 and especially from 33:1 to 10:1.

Suitably the composition contains for example, from 0.05 to 85%, preferably from 0.5 to 50%, more preferably from 1 to 30% and especially from 1 to 10% by weight, based upon the total weight of the composition of water-soluble cellulose ethers.

The composition may contain from 0.01mg to 1g of Agent. Suitably the composition contains a daily dose of the Agent in a quantity sufficient to provide the desired therapeutic benefit. Suitable quantities of the Agent include, for example 10, 15, 25, 50, 75, 100, 125, 150, 200, 250, 300, 350, 400, 450, 500 or 550mg, depending upon the dose required and the particular form of the pharmaceutical composition. In a preferred embodiment the composition contains 100, 150, 250 or 500mg of the Agent, especially 250mg of the Agent.

The Agent may be used in the free base form or as a pharmaceutically acceptable salt, such as a pharmaceutically acceptable mono- or di-acid-addition salt with, for example, an

inorganic or organic acid, for example hydrochloric acid. Preferably the agent is in the free base form.

Typically the Agent will be present in an amount within the range of from 1 to 99%, and preferably from 1 to 70%, for example from 5 to 65% and especially from 10 to 60% by weight of the composition.

In another embodiment of the present invention the composition comprises:

(a) the Agent;

(b) a wetting agent; and

(c) a water-soluble cellulose ether.

We have found that a combination of a wetting agent and a water-soluble cellulose ether in the composition further reduces the rate of precipitation of the Agent from solution at pH values similar to that found in the lower GI tract.

Suitable wetting agents include pharmaceutically acceptable surface active materials, for example pharmaceutically acceptable surfactants, which may be ionic or non-ionic.

Suitable pharmaceutically acceptable non-ionic surfactants include, for example, polyethylene glycols; polyoxyethylene-polypropylene glycols for example Poloxamer 68; polyethyleneglycol esters and ethers, for example polyethoxylated castor oil (for example Cremophor EL), polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil, or polyethoxylated fatty acid from hydrogenated castor oil; ethoxylated stearic acid, for example Solutol HS15; polyoxyethylene sorbitan fatty acid esters, such as Polysorbate 80; polyethylene glycol sorbitan monooleates (such as Tween 80); polyoxyethylene sorbitan monostearates (such as Tween 60), polyoxyethylene sorbitan monopalmitates (such as Tween 40), polyoxyethylene sorbitan monolaurates (such as Tween 20); and ethylene oxide-propylene oxide copolymers, for example ethylene oxide-propylene oxide block copolymers (such as Pluronics or Tetronics).

Suitable pharmaceutically acceptable ionic surfactants may be anionic, cationic or zwitterionic. Suitable anionic surfactants include, for example, alkyl and aryl sulphonates, sulphates or carboxylates, such as an alkali metal salt of a (8-20C)alkyl sulphate, sulphonate or carboxylate, for example, sodium dodecyl sulphate (sodium lauryl sulphate), potassium myristate, sodium laurate or sodium lauryl sulphonate; di-alkyl sulphoscuccinates, preferably in the form of an alkali metal salt, for example sodium, calcium or potassium dioctyl sulphosuccinate (e.g. Docusate sodium or Aerosol OT) or sodium diamyl sulphosuccinate (Aerosol AY); bile acid salts, such as salts of deoxycholic acid, taurocholic acid, or

glycocholic acid, preferably alkali metal salts of bile acids, for example a sodium salt of a bile acid such as sodium taurocholate, sodium deoxycholate or sodium glycocholate; anionic water-dispersible cellulose derivatives, such as anionic water-dispersible cellulose ethers, for example carboxymethyl cellulose and salts thereof. Suitable cationic surfactants include for example quaternary ammonium compounds such as alkylammonium compounds (preferably (8-20C)alkylammonium compounds) for example laurylammonium chloride, alkyltrimethyl ammonium compounds (preferably (8-20C)alkyltrimethyl ammonium compounds) for example cetyltrimethylammonium bromide, trimethyltetradecylammonium bromide or benzalkonium halides ((8-20C)alkylbenzyldimethylammonium halides), for example benzalkonium chloride; (8-20C)alkylpyridinium compounds, for example cetylpyridinium chloride. The composition may contain a single wetting agent or two or more wetting agents.

Preferably the wetting agent is selected from an anionic and non-ionic surfactant , or a combination thereof. More preferably the wetting agent is an alkali metal (8-20C)alkyl sulphate, more preferably an alkali metal dodecyl sulphate. It is especially preferred that the wetting agent is sodium dodecyl sulphate.

The wetting agent may be present in the composition according to the present invention at a concentration below the critical micelle concentration (CMC) of the wetting agent. We have found that the wetting agent inhibits precipitation of the Agent from solution at pH values similar to those in the GI tract where the Agent is absorbed (such as the upper intestine). This is surprising because the wetting agent is at a concentration below the CMC required for solubilisation of the Agent by micelle formation.

The CMC for a particular wetting agent in an aqueous environment may be readily determined using standard techniques, for example using the Wilhelmy plate method (see for example S.A Hagan, A.G.A Coombes, M.C. Garnett, S.E. Dunn, M.C. Davies, L. Illum and S.S. Davis, Langmuir 1996, 12, 2153-2161).

A suitable weight ratio of Agent to wetting agent is from 1:2 to 500:1, preferably from 1:1 to 300:1, more preferably from 100:1 to 250:1 and especially from 150:1 to 200:1.

Suitably the composition will contain from 0.01 to 10%, for example from 0.05 to 5%, preferably from 0.1 to 1% and especially from 0.1 to 0.5% by weight of the wetting agent.

Preferred water-soluble cellulose ethers in this embodiment are as hereinbefore defined in relation to the first aspect of the invention.

Suitable quantities of Agent and water-soluble cellulose ether in the composition are as described herein.

In view of the foregoing, a preferred composition according to this embodiment of the invention comprises:

(a) from 1 to 99 (preferably from 10 to 98) parts the Agent;

(b) from 0.01 to 10 (preferably from 0.05 to 5) parts of a wetting agent (preferably an anionic surfactant, for example sodium dodecyl sulphate) ; and

(c) from 0.1 to 90 (preferably from 0.5 to 85) parts of a water-soluble cellulose ether (preferably hydroxypropylmethyl cellulose);

wherein all parts are by weight and the sum of the parts (a)+(b)+(c)=100.

The water-soluble cellulose ether present in the composition according to the invention may be used as, for example fillers, binders, disintegrants or film coatings as, for example, described hereinafter.

Optionally additional excipients may be included in the pharmaceutical composition according to the present invention. Additional excipients which may be present include for example, one or more fillers (diluents), binders, disintegrants or lubricants.

Accordingly a further embodiment of the invention provides a pharmaceutical composition comprising the Agent, a wetting agent and one or more fillers, binders, disintegrants or lubricants. A still further embodiment of the invention provides a solid pharmaceutical composition for oral administration comprising the Agent, a wetting agent one or more fillers, one or more binders, one or more disintegrants and one or more lubricants.

Suitable fillers include, for example, lactose (which may be in an anhydrous or hydrated form, for example lactose monohydrate), sugar, starches (for example corn, wheat, maize, potato), modified starches (for example as starch hydrolysates or pregelatinized starch which may be thermally, mechanically or chemically modified), microcrystalline starches, mannitol, sorbitol, trehalose, maltose, inorganic salts (e.g. calcium carbonate, magnesium carbonate, dibasic calcium phosphate (anhydrous/dihydrate), tribasic calcium phosphate), cellulose, cellulose derivatives (e.g. microcrystalline cellulose), calcium sulphate, xylitol and lactitol.

Suitable binders include, for example, polyvinylpyrrolidone (for example povidone K25-32), lactose (which may be in an anhydrous or hydrated form, for example lactose monohydrate), starches, modified starches, sugars, gum acacia, gum tragacanth, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and salts thereof (for example sodium carboxymethylcellulose), hydroxypropyl methylcellulose,

hydroxyethyl cellulose, hydroxypropyl cellulose, copolyvidone, gelatin and alginates (for example sodium alginate).

Suitable disintegrants include, for example, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycolate, starches, microcrystalline cellulose carboxymethylcellulose and salts thereof (for example sodium or calcium carboxymethylcellulose), hydroxypropyl methylcellulose, hydroxypropyl cellulose (preferably low substituted hydroxypropyl cellulose i.e. hydroxypropyl cellulose containing approximately 5 to 16% by weight hydroxypropoxy groups) or alginic acid.

Suitable lubricants include, for example, magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols, sodium lauryl sulphate and sodium stearyl fumarate.

Further additional excipients which may be added include preservatives, stabilisers, anti-oxidants, silica flow conditioners, antiadherents or glidants.

Other suitable fillers, binders, disintegrants, lubricants and additional excipients which may be used are described in Handbook of Pharmaceutical Excipients, 3rd Edition (2000), American Pharmaceutical Association; The Theory and Practice of Industrial Pharmacy, 3rd Edition, Lachman et al. 1986; Pharmaceutical Dosage Forms: Tablets Volume 1, 2nd Edition, Lieberman, Hebert A., et al, 1989; Modern Pharmaceutics, Banker, Gilbert and Rhodes, Christopher T, 3rd edition, 1995; and Remington's Pharmaceutical Sciences, 20th Edition, 2000.

Suitably one or more fillers will be present in an amount of from 10 to 90% by weight, for example from 30 to 50% by weight.

Suitably one or more binders will be present in an amount of from 0.5 to 50% by weight, for example from 0.5 to 10% by weight.

Suitably one or more disintegrants will be present in an amount of from 0.5 to 20%, for example from 1 to 10% by weight.

Suitably one or more lubricants will be present in an amount of from 0.1 to 5% by weight, for example from 0.5 to 3% by weight.

It will be appreciated that a particular excipient may act as a both a binder and a filler, or as a binder, filler and disintegrant. Typically the combined amount of filler, binder and disintegrant comprises, for example 40 to 80% by weight of the composition.

In a further embodiment the composition according to the present invention comprises:

(a) from 10 to 80 parts of the Agent;

(b) from 0.05 to 5 parts wetting agent selected from an anionic surfactant (preferably sodium dodecyl sulphate);

(c) from 10 to 60 parts of one or more fillers selected from lactose (preferably lactose monohydrate), mannitol and microcrystalline cellulose;

(d) from 1 to 10 parts of one or more disintegrants selected from carboxymethylcellulose sodium, carboxymethyl cellulose calcium, croscarmellose sodium, crospovidone and sodium starch glycolate ;

(e) from 1 to 20 parts of a binder selected from a polyvinylpyrrolidone (preferably povidone (preferably K29-32) and hydroxypropylmethylcelullose (preferably grades, 1828, 2208, 2906 and especially 2910 having a viscosity of from 2 to 18 cps as described hereinbefore); and

(f) 0 to 3 parts of a lubricant (preferably magnesium stearate);

wherein all parts are by weight and the sum of the parts (a)+(b)+(c)+(d)+(e)+(f)=100, and wherein at least one of the components selected from (d) or (e) contains a water-soluble cellulose ether selected from hydroxypropylmethylcelullose and carboxymethylcellulose sodium.

In this embodiment it is preferred that component (e) of the composition contains hydroxypropylmethylcelullose.

In a preferred embodiment the pharmaceutical composition of the invention is formulated into an oral dosage form, more preferably a solid dosage for oral administration, still more preferably a solid dosage for daily oral administration, for example a tablet, pellet, granule or capsule formulation.

When the pharmaceutical composition according to the invention is a solid dosage form such as a tablet, pellet or granules the solid composition optionally further comprises a suitable coating, for example a film coating. A coating can be used to provide protection against, for example, moisture ingress or degradation by light, to colour the formulation, or to modify or control the release of the Agent from the formulation.

Suitable coatings such as film coatings, that may be applied to the composition according to the invention comprise a film forming agent, for example a sugar or more preferably a film forming polymer. Suitable sugar coatings are well known and comprise for example sucrose or lactose. Suitable film forming agents include, for example film forming polymers, such as cellulose ethers, esters and mixed ethers and esters, for example hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylcellulose,

methylcellulose, hydroxypropylmethylcellulose acetate succinate or hydroxypropylmethylcellulose phthalate; film-forming acrylic polymers, for example methacrylate-methylmethacrylate copolymers; and film forming vinyl polymers, for example polyvinyl alcohols or polyvinyl acetate phthalate. Preferably the film-forming polymer is a water-soluble film-forming polymer, more preferably a water-soluble cellulose ether for example hydroxypropylmethlycellulose (preferably hydroxypropylmethyl cellulose with a viscosity of from 2 to 18cps (measured in a 2%w/v solution at 20°C) and selected from, for example grades 1828, 2208, 2906 and especially 2910 as defined hereinbefore). The amount of film-forming agent used will depend upon the desired properties of the film coating. Generally the film forming agent will be present in an amount of from 40 to 90% by weight of the film coating, for example from 50 to 80% of the film coating. The film forming agent is typically present at from 0.5 to 5%, preferably 1 to 3% by weight of the formulation according to the invention.

Optionally the film coating contains additional components such as plasticiser, colorants, dispersion aids and opacifiers. Plasticisers may be used to improve film flexibility and durability and adhesion properties of the film coating. Suitable plasticisers include, for example glycerin, acetylated monoglycerides, citrate esters (for example triethyl citrate), propylene glycols, polyethylene glycols (for example polyethylene glycols with a molecular weight of from 200 to 500, preferably 300), triacetin, triglycerides (for example castor oil), or phthalate esters (for example diethylphthalate). Generally the plasticiser, when used, is present in an amount of from 1 to 20%, for example 5 to 15% by weight based upon the weight of the film coating.

Suitable opacifiers and colorants are well known and include for example titanium dioxide, ferric oxides (for example iron oxide).

Suitable dispersion aids include, for example talc.

In an embodiment of the invention the film coating comprises

(i) from 50 to 100 (preferably from 50 to 80 parts of a water-soluble cellulose ether (preferably hydroxypropylmethycellulose, more preferably hydroxypropylmethyl cellulose with a viscosity of from 2 to 18cps (measured in a 2%w/v solution at 20°C), for example grades 2910, 1828, 2208 or 2906 as defined hereinbefore with a viscosity of from 5 to 7cps);

(ii) from 0 to 25 (preferably from 5 to 20) parts plasticiser (preferably polyethylene glycol, more preferably polyethylene glycol with a molecular weight of from 200 to 500); and

(iii) from 0 to 50 (preferably from 0 to 30) parts in total of opacifiers (preferably titanium dioxide) , colorants (preferably an iron oxide) and dispersion aids;

wherein all parts are by weight and the sum of the parts (i)+(ii)+(iii) = 100.

The coating may comprise, for example, 0.5 to 10% by weight of the composition, particularly 1 to 6%, and preferably 2 to 3%.

In one preferred embodiment of the invention the pharmaceutical composition comprises a solid pharmaceutical composition (such as a tablet, pellet or granule formulation) comprising:

(i) a core comprising the Agent; and

(ii) a coating comprising a water-soluble cellulose ether.

In this embodiment preferred water-soluble cellulose ethers are as hereinbefore described, especially hydroxypropylmethylcellulose (preferably grades, 1828, 2208, 2906 and especially 2910 having a viscosity of from 2 to 18 cps). Preferably the coating is applied as a film coating as herein described. The core containing the Agent may comprise any of the compositions described hereinbefore containing a water-soluble cellulose ether (and optionally other additional excipients as hereinbefore described). Alternatively, the core may comprise the Agent without a water-soluble cellulose ether (and optionally other additional excipients as hereinbefore described). Accordingly, in this embodiment the water-soluble cellulose ether may be present entirely in the coating. Alternatively, water-soluble cellulose ether(s) may be present in both the core and the coating.

In an especially preferred embodiment the composition according to the present invention is a tablet, pellet or granule suitable for oral administration, comprising a core coated with a film coating wherein the core comprises:

from 45 to 55% of the Agent (preferably in free-base form);

from 25 to 40% lactose (preferably lactose monohydrate);

from 5 to 15% microcrystalline cellulose;

from 2 to 6% disintegrant (preferably croscarmellose sodium);

from 1 to 5% povidone (preferably K29-32);

from 0.05 to1% (preferably 0.1 to 0.5%) sodium dodecyl sulphate; and

from 0.1 to 4% lubricant (preferably magnesium stearate);

and wherein the film coating comprises:

from 0.5 to 3% water-soluble cellulose ether (preferably hydroxypropylmethyl cellulose, more preferably grade 2910, with a viscosity of from 5 to 7cps);

from 0 to 0.5% (preferably from 0.05 to 0.5%) plasticiser (preferably polyethylene glycol, more preferably polyethylene glycol with a molecular weight of 200 to 500, especially 300);

from 0 to 0.5% (preferably 0.1 to 0.4%) dispersion aid (preferably talc);

from 0 to 0.5% (preferably 0.1 to 0.4%) opacifier (preferably titanium dioxide); and

from 0 to 0.5%, (preferably from 0.001 to 0.4%) colorant (preferably iron oxide);

wherein all % are by weight based upon the total weight of the composition.

The pharmaceutical composition of the invention may be prepared, using standard techniques and manufacturing processes generally known in the art, for example by dry blending the components or, preferably, wet granulation techniques followed by compression to form a tablet or filling into suitable capsules. A suitable wet granulation technique comprises for example, blending together the Agent, one or more fillers, all or a portion of a disintegrant and optionally the water-soluble cellulose ether, wetting agent and/or one or more binders, as well as other additional excipients if desired, using, for example a granulator. The resulting powder blend is then granulated with a small volume of purified water, optionally containing wetting agent and/or one or more binders (which may be a water-soluble cellulose ether). The granulate is passed through a screen, to break up large aggregates, dried and passed though a mill. Any remaining disintegrant and a lubricant are then added to the milled granulation and after blending the resultant homogeneous mixture is compressed into tablets. Alternatively, the milled granulate is filled into a suitable capsule to provide a capsule formulation.

A suitable dry blending technique comprises for example, blending together the Agent, the water-soluble cellulose ether and optionally wetting agent, one or more fillers, one or more binders and one or more disintegrants, as well as other additional excipients if desired. The components of the blend prior to blending, or the blend itself, may be passed through a mesh screen, for example a 400-700 μm mesh screen. A lubricant, which may also be screened, is then added to the blend and blending continued until a homogeneous mixture is obtained. The mixture is then compressed into tablets. Alternatively, the mixture may be filled into suitable capsules to provide a capsule formulation.

It will be appreciated that modifications of the dry blending and wet granulation techniques, including the order of addition of the components and their screening and blending prior to compression into tablets, may be carried out according to principles well known in the art.

When the composition is coated, for example with a film coating the coating may then be applied using conventional methods, for example by coating with a film coating formulation, preferably a water-based film coating formulation. The film-coating formulation may be applied to the composition according to the present invention by, for example, spray coating or fluidised bed coating. The provision of a film coating comprising a water-soluble cellulose can be used to provide the cellulose ether present in the composition according to the present invention.

When the composition is prepared as a capsule formulation the composition is first prepared as a powder or granules and is then filled into a capsule to provide a capsule formulation, suitable capsules are well known in the art. For example, hard gelatin, water-soluble cellulose ether (for example hydroxypropylmethylcellulose) and starch capsules. When the capsule contains a water-soluble cellulose ether, the capsule may be used to provide the water-soluble cellulose ether present in the composition according to the invention.

A further aspect of the present invention provides a method of preparing a pharmaceutical composition which comprises admixing the Agent with a water-soluble cellulose ether and optionally other excipients, wherein the Agent, water-soluble cellulose ether and optional excipients are as hereinbefore described in relation to the first aspect of the invention.

A further aspect of the present invention provides a method for inhibiting the rate of precipitation of the Agent from aqueous solution in the GI tract of a patient in need of the Agent, comprising orally administering to said patient a composition according to the first aspect of the present invention.

A further aspect of the present invention provides the use of a composition according to the first aspect of the invention in the manufacture of a medicament for inhibiting the rate of precipitation of the Agent from aqueous solution in the GI tract of a warm blooded mammal (preferably a human).

A further aspect of the present invention provides a method for reducing inter-patient variability in bioavailability and/or plasma concentrations of the Agent in a patient in need of

the Agent comprising orally administering to said patient a pharmaceutical composition according to the first aspect of the present invention.

A further aspect of the present invention provides the use of a pharmaceutical composition according to the first aspect of the present invention in the manufacture of a medicament for reducing inter-patient variability in bioavailability and/or plasma concentrations of the Agent.

The invention is illustrated below by the following non-limiting examples, wherein the Agent is in the free base form of formula I.

In the Examples the following abbreviations have been used:

HPLC: High pressure liquid chromatography

ACN: Acetonitrile

Example 1: Coated Tablet Formulation

Tablet core	
The Agent	250.0 mg
Lactose monohydrate	163.5 mg
Microcrystalline cellulose	50.0 mg
Croscarmellose sodium	20.0 mg
Povidone	10.0 mg
Sodium lauryl sulphate	1.5 mg
Magnesium stearate	5.0 mg
Tablet coating	
Hydroxypropyl methylcellulose[1]	8.16 mg
Polyethylene glycol 300	1.60 mg
Talc	1.18 mg
Titanium Dioxide	1.18 mg
Yellow ferric oxide	0.04 mg

Footnote [1] Grade 2910, 6cp viscosity (measured at 2%w/v at 20°C) ex Shin Etsu).

The example formulation was prepared by conventional wet granulation, compression and film coating processes. The Agent, lactose monohydrate, microcrystalline cellulose and

croscarmellose sodium were mixed together in a high shear granulator to produce a homogeneous mix. An aqueous solution of the povidone and sodium lauryl sulphate was then added to the powders with mixing until a suitable wet mass was obtained. The wet granules were passed through a suitable screen to remove large particles, then dried. The dried granules were then passed through a further screen and blended with pre-milled magnesium stearate. The resultant granules were compressed into tablet cores, which were then coated using a conventional pan coater. The film coat was applied by spraying an aqueous suspension of the hydroxypropyl methylcellulose, polyethylene glycol 300, talc, titanium dioxide and yellow ferric oxide onto the tablet cores.

The tablets were tested using the pH shift precipitation method detailed below.

Example 2 Coated Tablet Formulation

Tablet core

The Agent	250.0 mg
Lactose monohydrate	163.5 mg
Microcrystalline cellulose	50.0 mg
Croscarmellose sodium	20.0 mg
Povidone	10.0 mg
Sodium lauryl sulphate	1.5 mg
Magnesium stearate	5.0 mg
Tablet coating	
Hydroxypropyl methylcellulose[2]	7.65 mg
Polyethylene glycol 300	1.5 mg
Titanium Dioxide	0.50 mg
Yellow ferric oxide	0.90 mg
Red ferric oxide	0.90 mg

Footnote [2]: Grade 2910, 6cp viscosity (measured at 2%w/v at 20°C) ex Shin Etsu)

The formulation described above was prepared using an analogous wet granulation, compression and film coating method to that described in Example 1.

The tablets were tested using the pH shift precipitation method detailed below.

pH Shift Precipitation Method

The formulations described in the examples above were dissoluted in media comprising 500ml 0.07N HCl (approximately pH 1.5) for one hour at 37°C (paddle speed 100 rpm). A 5 ml sample was taken at 60 minutes and the media replaced. HPLC analysis (described below) of this sample confirmed that 100% of the Agent was in solution.

10ml of a 2.5M KH_2PO_4 / 16.72% (w/v) NaOH solution was then added to shift the pH to 6.5. 5ml samples were then removed with a plastic syringe at 2, 5, 15, 30, 45 and 60 minutes after pH adjustment and media replaced after every sampling time point. Each sample was centrifuged (14,000rpm) at ambient temperature for 15 minutes and then analysed by HPLC using the following conditions:

Eluent:	38% ACN / 62% water / 0.6% ammonium acetate
column:	10 cm x 3 mm (internal diameter) INERTSIL ODS-3[3]. (with guard)
detection wavelength:	247 nm
flow rate:	0.9 ml/min
injection volume:	20 µl

Footnote [3]: column ex Hichrom containing 3µm beads.

Comparative Example 1

The pH shift precipitation method described above was repeated but using 250mg of the Agent alone.

Results

Figure 1 shows the pH shift precipitation profiles for the formulations detailed in Examples 1 and 2 and comparative Example 1. The results demonstrate that the rate of precipitation of the Agent following shift of pH to 6.5 is slower for the compositions according to the present invention (Examples 1 and 2) than for the Agent alone, indicating that supersaturation is maintained for longer when the Agent is included in a composition according to the present invention.

The pH shift precipitation test simulates the effect of the change from low pH to high pH as the Agent moves from the acid environment of the stomach into the alkaline environment of the upper intestine which is thought to be the site of highest intrinsic absorption of the Agent. Figure 1 clearly shows that the composition according to the present

invention significantly reduces the rate of precipitation. This would be expected to give an improvement in pharmacokinetic properties for example, increased absorption and/or bioavailability and may reduce inter-patient variability in the bioavailability and/or plasma concentration of the Agent.

CLAIMS

1. A pharmaceutical composition comprising 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline or a pharmaceutically-acceptable salt thereof (the "Agent") and a water-soluble cellulose ether.

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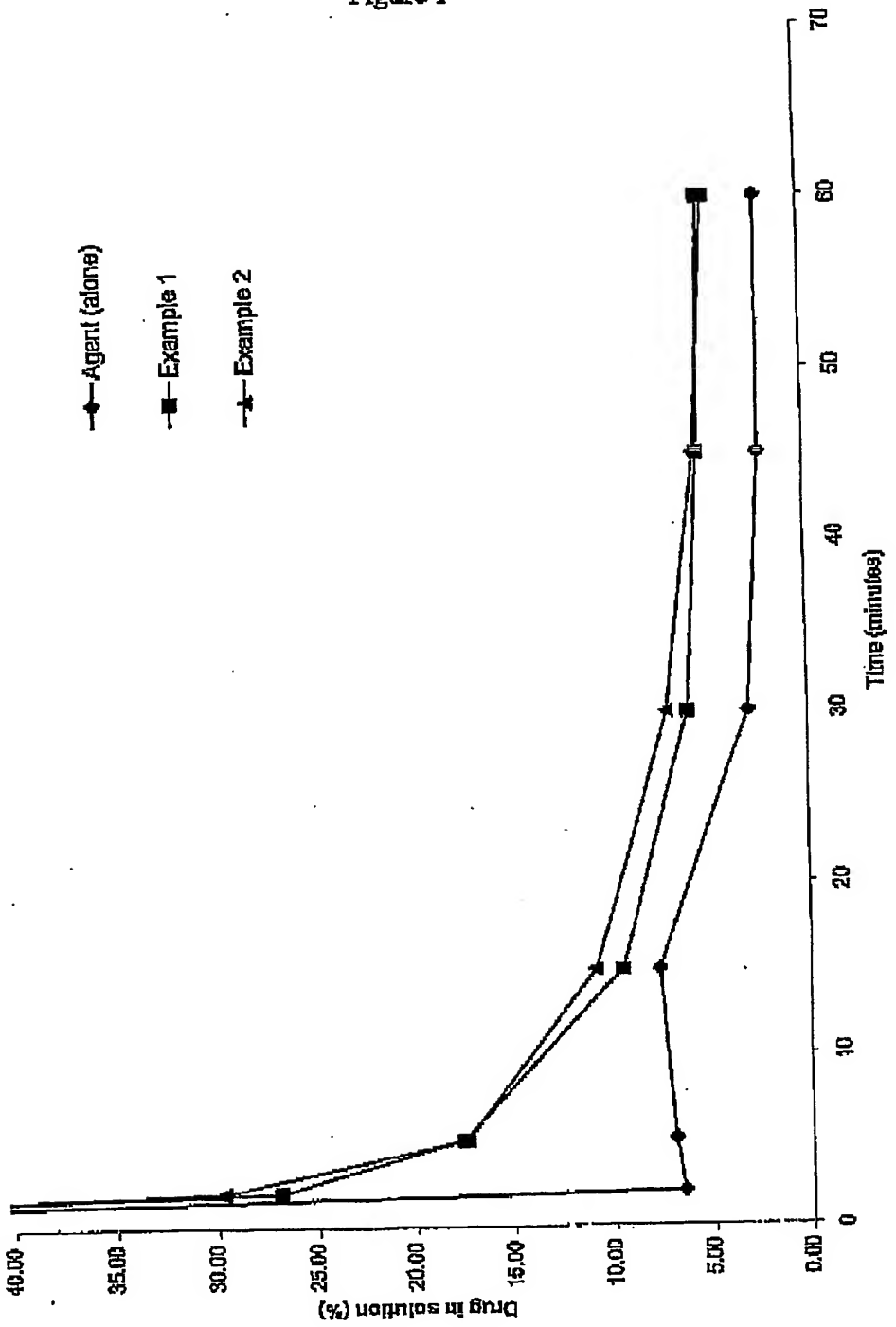
Figure 1



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